have hereinabove canceled claims 53-77 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed application and added new claims 78-99. Support for these claims may be found inter alia in the specification as follows: claims 78-79: page 11, lines 13-15, page 76, lines 19-21, and page 32, lines 1-20; claims 80-81: page 12, lines 28-31; claim 82: page 12, lines 15-16; claims 83-87: page 13, lines 8-26; claims 88-90: page 14, lines 1-5; claim 91: page 43, lines 4-9, and page 53, line 35 to page 54, line 1; claim 92: see support for claims 78-79, and page 15, lines 11-22; claim 93: see support for claims 78-79, and page 73, lines 15-18; claim 94: see support for claims 78-79, and and page 15, line 26 to page 16, line 20; claims 95-97: page 17, lines 5-10; claim 98-99: page 18, lines 5-10. Accordingly, claims 78-99 do not involve any issue of new matter such that entry of this amendment is respectfully requested.

Figure 6B

The Examiner stated that the prior objection to the disclosure is maintained for the reasons as set forth in the last Office Action mail 6/10/96 (see Paper No. 9). The Examiner stated that applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. The Examiner stated that until applicants submit a proper Figure said objection is maintained.

In response, applicants will consider submitting a new Figure 6B upon the indication of allowable subject matter.

Obviousness-type double patenting rejection

The Examiner provisionally rejected claims 53-77 under the judicially created doctrine of obviousness-type, double patenting as being unpatentable over the claims 53, 55-57 and 59-77 of

copending Application No. 08/474,784.

The Examiner stated that applicants assert that the added new claims in the copending application obviate the obvious type double patenting. The Examiner stated that applicants' arguments are not persuasive since the claims of the instant application encompass conjugating the ceramide portion of GM2 via a variety of linkages as recited the claims in copending application. The Examiner stated that applicants amendments are insufficient to remove the rejection. The Examiner stated that even if applicants limited the '784 application to remove GD2, it is noted that the conjugated of other gangliosides would be obvious over the each other because they all have similar base structure and are derived from GM3 as indicated by Ritter et al. (Cancer Biology, 1991) or record.

The Examiner stated that claims 53-77 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 44 and 46-56 of copending Application Nos. 08/477,147 and 08/481,809.

The Examiner stated that although the conflicting claims are not identical, they are not patentably distinct from each other fro the reasons set forth in the prior Office actions. The Examiner stated that applicants' amendments are insufficient to overcome the double patenting rejection in regard to 08/481,809 or 08/477,147.

The Examiner stated that claims 53-77 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 69-96 of copending Application Nos. 08/196,154.

The Examiner stated that the instantly claims compositions drawn to specific species of ganglioside conjugated to KLH anticipate the

broader claims of 08/196,154.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claims 53-77 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed application. Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim 56

The Examiner objected to claim 56 under 37 C.F.R. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner stated that applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The Examiner stated that the claim does not further limit the protein-based carrier of claim 53. The Examiner stated that correction is required.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claim 56 without prejudice or disclaimer to their right to pursue the subject matter of this claim in a later-filed application. Applicants contend that this amendment obviates the above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 53-57, 59-72 and new claims 73-77 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described it the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mails 6/10/96 (see Paper No. 9).

The Examiner stated that applicants arguments' have been carefully considered. The Examiner stated that applicants again argue make and test. The Examiner stated that this is again not persuasive for reasons already extensively made of record in the previous response and reiterated below.

The Examiner stated that protein chemistry is probably one of the most unpredictable areas of biotechnology. The Examiner stated that for example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al.). The Examiner stated that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). The Examiner stated that Rudinger et al. teaches "particular amino acids and sequences for different aspects of biological activity can not be predicted a priori but must be determined from case to case by painstakingly experimental study" (see page 6). The Examiner stated that Salgaller et al. teach modifications (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein.

The Examiner stated that Fox et al. teach methods for determining fragments which have antigenic activity is unpredictable. The Examiner stated that these references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. The Examiner stated that in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad or derivatives and fragments encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

The Examiner stated that contrary to applicants arguments it is reasonable to conclude an undue burden is required to screen for positions within the sequence where amino acid modifications (i.e. additions, deletions, or modifications) can be made with a reasonable expectation of success in obtaining similar activity/utility are limited and the result of such modifications is unpredictable as exemplified by the teachings of Lazar et al., Burgess et al., Rudinger et al., and Salgaller et al. The Examiner stated that these references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein.

The Examiner stated that the specification does not support the broad scope of the claims which encompass a multitude of analogs or equivalents because the specification does not disclose the following: the general tolerance to modification and extend of such tolerance; specific positions which can be predictably modified; and the specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful. The Examiner stated that thus, applicants have not

provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims broadly including any number of deletions, additions, and/or substitutions of any size. The Examiner stated that scope of the claims must bear a reasonable correlation with the scope of enablement (in re Fisher, 166 USPQ 19 24 (CCPA 1970)). The Examiner stated that without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The Examiner stated that see Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

The Examiner stated that applicants cite to page 12, lines 4-13 of the specification for support of using derivatives of KLH. The Examiner stated that said disclosure id not commensurate in scope with the claims invention. The Examiner stated that said cite makes reference only to linking KLH to an "immunological adjuvant" and not amino acid modifications (i.e. deletions, substitutions) of KLH. The Examiner stated that as set forth above the scope of the claims must bear a reasonable correlation with the scope of enablement (in re Fisher, 166 USPQ 19 24 (CCPA 1970)). The Examiner stated that for the reason set forth above and in the last Office Action said rejection is maintained.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the claimed invention was enabled. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claims 53-77. Applicants contend that the invention of newly submitted claims 78-99 is enabled. Applicants contend that this amendment obviates the above rejection and respectfully request that the examiner

reconsider and withdraw this ground of rejection.

Claims 67-72

The Examiner stated that as to claims 67-72, the claims are enabled for the use of the composition only for the treatment of cancer but are not enabled for the prevention of cancer, for reasons made of record in Paper No. 16, mailed 7-11-97.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that a claim directed to the prevention and treatment of a cancer using the subject composition is fully enabled. In support of claims concerning the treatment and/or prevention of the cancer, applicants attach hereto as **Exhibit A** a copy of the following paper: Helen Zhang et al "Antibodies against GD2 Ganglioside Can Eradicate Syngeneic Cancer," Cancer Research 58: 2844-2849 (1998). This paper demonstrates that the conjugated vaccine of the subject invention prevents the outgrowth of micrometastases (see page 2844, first column). The paper shows that the conjugated vaccine prevents establishment of subsequently administered EL4 challenge (which is a lymphoma), and eliminates EL4 micrometastases when administered after EL4 challenge (see page 2844, second column). The paper shows that mice receiving the conjugate vaccine survived significantly longer, and that one mouse did not show any evidence of tumor (see page 2845, second column). The paper teaches that the conjugated vaccine protects against tumor challenge and eliminates micrometastases. Applicants contend that this is support for the use of the composition to treat or prevent cancer. Applicants contend that these remarks obviate the above rejections and respectfully request that the Examiner reconsider and withdraw the rejection.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 53-77 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner stated that this is a new matter rejection.

The Examiner stated that applicants point to page 32, lines 13-18 and page 12 lines 22-26 for support for the now claimed invention. The Examiner stated that this is not persuasive, the passage at page 32, lines 13-18 provide for a specific coupling procedure at the C-4 carbon of the sphingosine moiety of the ceramide to the ϵaminolysyl group of a proteins (ozonolysis, production of a functional aldehyde group and coupling to an ϵ-aminolysyl group on a protein by reductive animation. The Examiner stated that the passage at page 12 lines 22-26 in combination with the passage at page 32, lines 13-18 does not support a broad coupling to any generic portion of the ceramide backbone of the ganglioside, by any generic means by cleavage of any double bond (i.e. C=O) and coupling to any portion of the ceramide, a concept that is now broadly claimed. The Examiner stated that applicants were clearly not in possession of that which is now broadly claimed. The Examiner stated that correction is required.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that they were in possession of the claimed invention at the time of filing. Nevertheless, without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claims 53-77 without prejudice or disclaimer to their

right to pursue the subject matter of these claims in a later-filed application. Applicants have also hereinabove added new claims 78-99. Applicants contend that this amendment obviates the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 53-66 and 68-77 under 35 U.S.C. §103(a) as being unpatentable over Livingston et al.(Cancer Research, 149:7045-7050, 1989) in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et all (Journal of Biological Chemistry 249(14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 182:32-43, 1990), Kensil et al. (The Journal of Immunology, 146(2):431-437, 1991), and Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al. (J. Biochem. 79(6):1253-1261, 1976).

The Examiner stated that Livingston et al. (Cancer Research) teach a composition administered to melanoma patients for stimulation the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2 (page 7046-7048). The Examiner stated that Livingston et al. teach that melanoma recurrence was delayed n patients developing GM2 antibodies after treatment with the composition (page 7048, paragraph 1 and column 2, paragraph 2). The Examiner stated that Livingston et al teach that more patients produced IgM antibodies than IgG antibodies to the GM2 (pate 7047, paragraph bridging columns 1-2). The Examiner stated that Livingston et al also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2). The Examiner stated that Livingston et al differ by not teaching the conjugate of the GM2 or other gangliosides by means of a carbon on the ceramide moiety with

aminolysyl groups on Keyhole Limpet Hemocyanin (KLH) in a composition and using this composition for treatment.

The Examiner stated that Ritter et al. (1991) teach IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response (page 406, paragraph 1). The Examiner stated that Ritter et al teaches discloses that the advantage of inducing an IgG antibody response vs IgM) against gangliosides is that IgG:1) has a higher affinity, b) is better able t penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, d) and is generally detectable in the serum for longer periods after immunization.

The Examiner stated that Liane et al. (Journal of Biological Chemistry, 249 (14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose of the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group of aminoethyl agarose of the amino group bearing glass beads.

The Examiner stated that Ritter et al (1990) teach that GD3 lactone is more immunogenic than GD3.

The Examiner stated that Livingston et al. (U.S. patent No. 5,102,663) teach that gangliosides GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3 are ganglioside that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1, lines 22-28).

The Examiner stated that Liane et al. (Journal of Biological Chemistry, 249(14):4460-4466, 1974) teach a method for covalent

coupling of ganglioside to aminoethyl agarose or the amino group bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e. the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group of aminoethyl agarose of the amino group bearing glass beads.

The Examiner stated that Kensil et al teach that QS-21 (i.e. the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4 and Figure 3). The Examiner stated that Kensil et al also teach that the immune responses obtained with QS-21 reached a plateau at doses between 10-80 ug in mice (page 433, column 1, paragraph 3).

The Examiner stated that Maricani et al tech the use of QS-21 adjuvant was useful because it did not cause a toxic reaction in cats (page 93, paragraph 1).

The Examiner stated that Uemura et al. (J. Biochem 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipid did not affect the haptenic reactivity of the ganglioside derivative with antibodies.

The Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the composition taught by Livingston et al by conjugating the GM-2 to KLH by covalently coupling GM2 to KLH by substituting GM2 for the globoside and KLH for the aminoethyl agarose t produce a GM-2-KLH conjugate by means of the olefinic bond of the sphingosine moiety of the GM2 (i.e. the instant ceramide double bond) and the ε-aminolysyl groups present in the KLH protein using the method of Liane et al. and add QS-21 as an adjuvant to the GM-2-KLH conjugate for use as a vaccine because the conjugated

composition would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al. (1991), thus providing the advantages by Ritter et al. 91991) and adding the QS-21 would be advantageous because it provides for a higher antibody response that the commonly used adjuvant use by Kensil et al and QS-21 provides the advantages that it is not toxic to animals as is taught by Marciani et al. The Examiner stated that it also would have been prima facie obvious to use doses of 10 and 80 ug of QS-21 in the composition and optimize the dose accordingly because the immune response with QS-21 plateaus at doses between 10-80 ug and optimization of the weight ratio of the components of the composition to provide an optimal response is well within the ordinary skill in the art and use the composition as modified supra for treatment of melanoma as taught by Livingston et al (Cancer Research). The Examiner stated that it also would have been prima facie obvious to one of ordinary skill in the art to substitute any one of GM3, GD2, GD3, or O-acetyl GD3 for the GM2 ganglioside in the composition and method as combined supra because they are all prominent cell-membrane components of melanomas as taught by Livingston et al. (U.S. Patent No. 5,102,663) and one of ordinary skill in the art would reach with the melanoma cells. The Examiner stated that it would have also been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the GD3 lactone for the GM2 ganglioside in the composition because GD3 lactone is more immunogenic then GD3, as taught by Ritter et al (1990) and would be expected to produce an enhanced antibody response as compared to GD3. The Examiner stated that optimization of the dosage, route immunization, number sites of immunization to administer the composition is will within the skill of the ordinary artisan.

The Examiner stated that one would have reasonably expected the conjugation procedure to work as substituted because conjugation

through the ε-aminolysyl groups of carrier proteins for enhance immunogenicity is routine in the art and Uemura et al (J. Biochem. 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipid did not affect the haptenic reactivity with antibodies.

The Examiner stated that claim 67 is rejected under 35 U.S.C. §103(a) as being unpatentable over Livingston et al. (Cancer Research) Ritter et al. (Cancer Biology 1991) Liane et al (Journal of Biological Chemistry 249(14):4460-4466, 1974), Livingston et al (U.S. Patent No. 5,102,663) Ritter et al. (1990), Kensil et al and Maricani et al. and Uemura et al (J Biochem 79(6):1253-1261, 1976) as applied to claims 18-20, 53, 55-67 and 69-72 above and further in view of Irie et al (U.S. Patent No. 4,557,931).

The Examiner stated that the teachings of Livingston et al (Cancer Research) Ritter et al. (Cancer Biology 1991), Liane et al (Journal of Biological Chemistry 24((14):4460-4466, 1974) Livingston et al (U.S. Patent No. 5,102,663) Ritter et al (190) Kensil et al and Marciani et al. and Uemura et al (J Biochem 79(6):1253-1261 1976) are set forth supra. The Examiner stated that the combination differs by not teaching the administration of the composition for treating cancer of epithelial origin or for producing antibodies to gangliosides found in the stroma of cancer.

The Examiner stated that Irie et al teaches that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31).

The Examiner stated that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer the GM-2-KLH conjugate /QS-21 composition or other ganglioside conjugate/QS-21 composition as combined supra to

patients afflicted with or susceptible to a recurrence of cancer of an epithelial origin (i.e. breast carcinomas) because the ganglioside GM-2 is found int eh stroma of the tumor as taught by Irie et al and one of ordinary skill in the art would expect that the antibodies produced by the composition react with the tumor and treat the disease.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the cited references do not render obvious the claimed invention. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled claims 53-77 without prejudice to their right to pursue the subject matter of these claims in a later-filed application. Applicants have hereinabove added new claims 78-99 which recite that the ganglioside derivative is conjugated to Keyhole Limpet Hemocyanin though a ceramide-derived carbon of the ganglioside derivative. Applicants contend that the cited references, alone or in combination, do not teach or suggest applicant's claimed invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

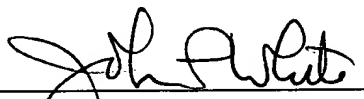
Summary

In view of the foregoing remarks, applicants respectfully request that the above grounds of rejection and objection be reconsidered and withdrawn and earnestly solicit allowance of the now pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee, other than the enclosed $640.00 fee which includes the $435.00 fee for a three-month extension of time and the $205 fee for additional claims, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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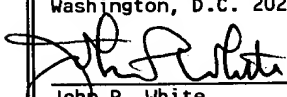
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



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John P. White Date
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